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Original Article

Evaluating Biliary Complications in Jaundiced Patients with Alcohol-Related Hepatitis: A Retrospective Study

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ABSTRACT

Introduction: This study aims to differentiate whether jaundice in patients with alcoholic hepatitis (AH) is due to alcohol-related liver disease or underlying biliary pathology, including choledocholithiasis, primary sclerosing cholangitis, primary biliary cholangitis, benign strictures, cholangiocarcinoma, or pancreatic cancer. Accurate differentiation is crucial for appropriate treatment decisions.

Methods: A non-interventional retrospective study examined patients admitted to our institute for presumed alcohol-related hepatitis management from 2016 to 2023. The primary outcome was the occurrence of biliary processes, whether benign or malignant, in patients managed for alcohol-related hepatitis within 90 days. Secondary outcomes assessed bilirubin level trends over seven days to evaluate steroid effects on alcohol-related hepatitis and predict underlying biliary processes. Variables were analyzed using bivariate and multivariate logistic regression with biliary process as the dependent variable.

Results: Our study revealed that patients with alcohol-related hepatitis and jaundice who had dilated common bile duct (CBD) or pancreatic duct (PD) on cross-sectional imaging were more likely to have biliary processes regardless of cholecystectomy history p-value 0.007 (CI 0.03-0.242) OR 7.5 and p-value 0.001 (CI 0.58-1.34), OR 1.2 respectively. However, there was no correlation between biliary process incidence and various demographic or clinical factors.

Conclusion: Cross-sectional imaging should be routinely used to evaluate biliary tree conditions in alcohol-related hepatitis patients with jaundice who have dilated CBD, particularly those with previous cholecystectomy or gallstones on imaging studies. This systematic approach enables early identification of underlying biliary issues and facilitates prompt, appropriate management decisions.

1. Introduction

Alcohol use disorder (AUD) and alcohol-related liver disease (ALD) are on the rise in the US. The average yearly prevalence of AUD was 9.4% of ED visits (9.3 million visits) between 2014 and 2018, and it gradually rose to 30% [1]. Alcohol-related cirrhosis rose by 43% during the same period, especially in young adults and women [2]. This coincided with an increase in mortality from alcohol-related liver disease along with improved screening for AUD [3]. AUD was further exacerbated by the COVID-19 pandemic in 2020. Alcohol sales rose from 7 billion dollars to 9 billion dollars [4]. This was believed to be due to a traumatic experience from the pandemic, financial insecurity, job loss, and lack of group support meetings like Alcoholics Anonymous (AA). ALD soon followed the trend with an increase in hospitalizations by 50% and an increase in mortality by 25% in many states [5, 6]. There is no unique presentation of ALD, and it can mimic many other liver disease presentations. Alcohol-related hepatitis (AH) per se can be present with few symptoms, with the distinct histopathological finding of alcohol steatohepatitis. American Association for the Study of Liver Disease (AASLD) provides guidance for diagnosis that categorizes patients into three groups: biopsy-proven AH, probable AH, and possible AH. Diagnosis criteria include pieces of patient history (high and long-term alcohol intake, recent development of jaundice) and labs consistent with AH (AST/ALT ratio > 1.5, Bilirubin > 3). Symptoms and signs of alcohol-related disease can overlap with drug-induced liver injury, viral hepatitis, ischemic hepatitis, and an autoimmune process [7]. Among the differentials are malignant and benign biliary obstruction with painless jaundice that is subacute. This includes exocrine pancreatic adenocarcinoma or cholangiocarcinoma, while benign causes may include choledocholithiasis, primary sclerosing cholangitis, or primary biliary cirrhosis. While alcohol abuse can suggest an alcohol-related process, this picture can be complicated by an increased risk of malignancy in alcohol users. Bile duct dysplasia was noted in native explanted livers in patients with either hepatitis C, alcohol, or both. This included low-grade and high-grade dysplasia, typically multifocal and more papillary than flat [8]. Also, alcohol liver disease was implicated in intrahepatic

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cholangiocarcinoma (ICC) development [9]. Specifically, Alcohol use > 80 grams daily was linked with a higher incidence of cholangiocarcinoma [10]. Tyson et al. demonstrated an association between intrahepatic and extrahepatic cholangiocarcinoma ECC [11]. A study in Italy of patients with Intrahepatic cholangiocarcinoma showed that the mean age was 65, 80% males, and 38% had cirrhosis, 23% reported alcohol use > 80 grams daily, but no significant association [12]. An increased risk of pancreatic cancer has also been associated with various types of hepatitis. Active HBV infection is linked with an increased risk of developing pancreatic cancer [13]. Low to moderate alcohol use was not strongly associated with pancreatic cancer risk; however, heavy use might be associated with increased risk [14]. In our study, we evaluated factors associated with malignant and benign biliary obstruction in patients who presented with painless jaundice in the setting of alcoholism. This will guide the need for a more thorough biliary workup in patients managed for suspected alcohol-related hepatitis.

2. Methods

2.1. Study design and patient cohort

This is a non-interventional retrospective study of all patients in the TidalHealth system located in Salisbury, Maryland, who were admitted and managed for presumed alcohol-related hepatitis from 2016 to 2023 (January until December). The Institutional Review Board (IRB) exempted the study in December 2023 with IRB review 1-1722687-1. Patient information was collected via an EPIC specialist who pulled the database. Specific diagnoses used were "alcoholic hepatitis" and "alcoholic liver disease". Our cohort included 186 patients who met our criteria based on AASLD guidelines. We excluded patients with missing data. We also excluded patients with alcohol liver disease but no active hepatitis after reviewing the charts.

2.2. Data collection

We gathered data from multiple variables that, in our opinion, reflect their comorbidities, risk factors for malignancy, their workup while admitted, including labs and imaging studies, steroid use while admitted, and finally, the incidence of benign biliary process and biliary cancer. This included data on age, gender, smoking history (any), chronic pancreatitis diagnosis, cirrhosis diagnosis, hepatitis B, and hepatitis C at baseline. Labs (serum bilirubin (day 0, 7), platelet count, serum alkaline phosphatase). Imaging (type of imaging, presence of dilated common bile duct CBD and pancreatic duct PD, presence of mass, presence of choledocholithiasis). Incidence of the biliary process (i.e., choledocholithiasis, PSC, PBC, benign strictures) and biliary cancer or related (cholangiocarcinoma, pancreatic adenocarcinoma, liver metastasis).

2.3. Outcome

The primary outcome measured was the occurrence of biliary events, benign or malignant, in patients who were managed for presumed alcohol-related hepatitis within 90 days of their first presentation. This was assessed based on cross-sectional imaging and liver biopsies collected from patient charts within 90 days of admission. Our secondary outcome was a bilirubin level trend over 7 days from admission to assess predictors of bilirubin improvement and whether that is related to a combination of biliary processes rather than merely alcohol-related hepatitis.

2.4. Statistical analysis

The statistical program SPSS 29.0 was used to analyze the data and find pertinent associations. Descriptive data were first assembled to determine the prevalence of different variables in the general population. The incidence of biliary processes was then used as the dependent variable in bivariate and multivariate logistic regression analyses. Furthermore, bilirubin levels were also used as the dependent variable in our study. 95% confidence intervals were generated, along with corresponding p-values. A two-tailed p-value of less than 0.05 was deemed statistically significant. We conducted a Mantel-Haenszel analysis using the incidence of biliary processes as the dependent variable. We evaluated the correlation with dilated CBD while stratifying for a history of cholecystectomy (CCY). Cholecystectomy can lead to physiological dilation of the CBD, so it was important to account for this as a confounding factor. Additionally, we performed a similar analysis stratified by both a history of stone disease and a history of CCY.

3. Results

3.1. Baseline Characteristics

A total of 186 patients with clinical jaundice and a history of significant alcohol use were included between 2016 and 2023. The mean age of the cohort was 50 years (range: 25–91 years), and 67% were male. A considerable percentage had comorbidities pertinent to hepatobiliary pathology: 72% were former smokers, and 44% suffered from cirrhosis. Roughly a third of the patients (33.9%) exhibited thrombocytopenia. Chronic hepatitis C occurred in 10% of cases, while chronic hepatitis B was present in 1.1% of cases. Cholecystectomy had been performed on only 13% of the individuals. Upon presentation, the average serum bilirubin level was 5.4 ± 6.5 mg/dL, showing minimal change after 7 days (5.3 ± 6.7 mg/dL), which reflects the mixed causes of jaundice. The average value of alkaline phosphatase was 161 ± 173 IU/L. Imaging showed that 14% of patients had a dilated CBD, whereas PD dilation was uncommon, occurring in only 1% of cases. Variables are described in **(Table 1)**.

3.2. Incidence of biliary process benign or malignant in patients with jaundice and alcoholism

We ran logistic regression and risk analysis with the incidence of the biliary process as a cause of jaundice as a dependent variable. This correlated with dilated CBD (CBD 6mm) with p-value 0.007 (CI 0.03 – 0.242) OR 7.5 and dilated PD 0.001 (CI 0.58 – 1.34) OR 1.2. However, no correlation with age p-value 0.445, gender p-value of 0.09, history of smoking p-value 0.58, cirrhosis status p-value of 0.81, history of cholecystectomy p-value 0.75, weight loss p-value 0.83, serum bilirubin on presentation p-value 0.28, platelets p-value 0.99, chronic hepatitis C p-value 0.08, serum alkaline phosphatase p-value 0.63, bilirubin response in one-week p-value 0.47. It is also described in **(Table 2)**.

3.3. Incidence of biliary process, benign or malignant, in correlation with dilated CBD stratified by whether the patient had a cholecystectomy

Using Chi-square and the Mantel-Haenszel formula, we found that a history of cholecystectomy increases the risk of biliary process in patients with dilated CBD by an odds ratio of 7, p-value 0.019.

3.4. The incidence of biliary process, benign or malignant, in correlation with dilated CBD, was stratified by whether the patient had CCY or a finding of stones on imaging (both suggest stone disease or a history of it in these patients)

Using Chi-square and the Mantel Haenszel formula, we found that a history of cholecystectomy or observing gallbladder stones on

Table 1: Baseline Characteristics of Study Subjects

Variable	Description
Age (mean, years)	50 (25–91)
Gender (male)	125 (67%)
Smoking (any history)	134 (72%)
Cirrhosis (present)	82 (44%)
Hx of CCY (present)	24 (13%)
Bilirubin (mg/dl) (day 0)	5.4 ± 6.5
Bilirubin (mg/dl) (day 7)	5.3 ± 6.7
Thrombocytopenia (present)	63 (33.9%)
Hepatitis C (chronic, present)	19 (10%)
Hepatitis B (chronic, present)	2 (1.1%)
Chronic pancreatitis (present)	4 (2.2%)
Alkaline phosphatase (IU/L) (day 0)	161 ± 173
Imaging studies (US, CS)	53 (28.5%), 109 (58.6%)
Dilated CBD (present)	26 (14%)
Dilated PD (present)	2 (1%)
Presence of stone disease	39 (21%)
Use of steroids (present)	21 (11.3%)
Malignant biliary process	2 (1.1%)

CCY, Cholecystectomy; US, Ultrasound; CS, Cross-sectional; CBD, Common bile duct; PD, Pancreatic duct.

imaging raises the risk of biliary pathology in patients with dilated CBD by an odds ratio of 6.9, p-value 0.03. The discovery of stones on imaging alone raised the risk of biliary processes in patients with dilated CBD, with an odds ratio of 5.8 and a p-value of 0.05. There was no correlation between the bilirubin trend between days 0 and 7 from presentation and steroid administration for alcohol-related hepatitis or with the incidence of an underlying biliary process. Our analysis did not show any significant correlation with steroid administration. This goes with current literature that failed to show significant improvement in clinical parameters in patients with severe alcohol-related hepatitis receiving steroids [15]. Our analysis also did not show any significant correlation between bilirubin improvement and incidence of a separate biliary etiology of jaundice (benign biliary processes (i.e., biliary stones) or malignant (i.e., cholangiocarcinoma)). This did not support our theory of the likelihood of a biliary process rather than alcohol-related hepatitis as a cause of jaundice in patients with sudden improvement in bilirubin or, conversely, failure to respond to steroids. The bilirubin trend, whether favorable or unresponsive to steroids, does not predict the likelihood of a biliary process.

4. Discussion

According to our research, patients suffering from alcohol-related hepatitis and jaundice, as well as those with a dilated CBD or PD, are more prone to have biliary processes, regardless of their history of cholecystectomy. These patients may require cross-sectional for further evaluation. Our study examined the relationship between

Table 2: p-values for Association Between Clinical and Laboratory Variables and Biliary Process

Variable	p-value
Age	0.445
Gender	0.09
History of smoking	0.58
Cirrhosis	0.81
Cholecystectomy	0.75
Weight loss	0.83
Serum bilirubin on presentation	0.28
Platelets	0.99
Chronic Hepatitis C	0.08
Serum alkaline phosphatase	0.63
Bilirubin response in 1 week	0.47

age, smoking status, gender, presence of cirrhosis, weight loss, hepatitis C and hepatitis B, and serum levels of platelets, serum alkaline phosphatase, and serum bilirubin with the occurrence of biliary processes. The absence of correlation between the incidence of biliary processes and various demographic and clinical factors presents noteworthy findings for our understanding of biliary pathophysiology. This is especially true for age. With increasing age, prior research indicates a higher occurrence of biliary diseases like gallstones. Various studies showed rates reaching up to 30% among women aged over 50, and a similar pattern was seen in aging men [16]. CBD dilation could be pathological. Determining the cause of CBD dilation is recommended in all symptomatic patients [17]. However, the approach to CBD dilation in asymptomatic patients is far from uniform in clinical practice. It is especially challenging in ALD, given underlying abnormal liver enzymes and elevated bilirubin, along with risk factors for developing biliary and pancreatic malignancy, mainly long-term alcohol intake. There are many obstructive (gallstones, malignancies) and non-obstructive (advanced age, opiate use, and prior cholecystectomy) etiologies of CBD dilation [18]. CCY has been a known cause of CBD dilation in some patients since 1887, as postulated by Oddi [19]. Residual or newly formed gallstones remain the most common long-term complication of cholecystectomy, as reported by Latenstein et al. [20]. Our study evaluated the significance of cholecystectomy, which leads to CBD dilation in alcohol-related hepatitis patients. Our analysis showed an odds ratio (OR) of 7 (p=0.019) in finding biliary pathology in alcohol-related hepatitis patients who had prior cholecystectomy with CBD dilation versus the same population with an intact gallbladder. This could be because patients with a history of cholecystectomy likely had gallbladder stone disease in the past, and they still carry the same risk factors to develop more stones. We recommend keeping a high clinical suspicion for concomitant biliary pathology in alcoholic hepatitis patients, even with a history of cholecystectomy.

We further analyzed patients with dilated CBD by stratifying them into subgroups differentiated by their CCY status or the presence of gallstones on imaging. We chose those two conditions to indicate these patients' potential stone disease history or current issues. Our analysis suggested that patients with a history of CCY or those with gallstones on imaging have a significantly increased risk of biliary

processes, as above. Such findings can increase the yield of further imaging to assess for any biliary complications in alcohol-related hepatitis patients. The main limitations of our study stem from its retrospective nature, which restricted our control over variables that could have influenced the observed associations. For instance, the decision to pursue imaging might have been biased by clinician judgment rather than patient presentation alone. The study included only 186 patients over seven years, limiting our findings' generalizability and statistical power, especially in multivariate analyses or subgroup stratifications. This small sample size may also increase the risk of Type II errors, where significant associations could be missed. Lastly, selection bias is a concern, as we only included patients with a presumed diagnosis of alcohol-related hepatitis based on coding. This may have inadvertently excluded patients with overlapping features or included those inaccurately diagnosed due to similar clinical and laboratory results.

5. Conclusion

The results of our research suggest that for patients with alcohol liver disease and jaundice who have dilated CBD, it is advisable to use cross-sectional imaging techniques to assess the condition of the biliary tree. This recommendation holds particularly true for those who have a medical history of cholecystectomy or for individuals with gallstones identified in imaging studies. This method enables early identification of underlying problems, which allows timely intervention and treatment.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

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Institutional Review Board (IRB)

This study was a non-interventional retrospective review of patients admitted for presumed alcohol-related hepatitis at TidalHealth Peninsula Regional, Salisbury, Maryland, from 2016 to 2023. The Institutional Review Board (IRB) of TidalHealth exempted this study in December 2023 (IRB review 1-1722687-1).

Large Language Model

None

Authors Contribution

QI and GA collected and interpreted data and drafted the manuscript; SI, JK, MS, UF, and CG interpreted data and drafted the manuscript; OK planned and conducted the study, collected and interpreted data, and drafted the manuscript. All authors reviewed and approved the final manuscript.

Data Availability

The data supporting this study's findings are available from TidalHealth Peninsula Regional, but restrictions apply. These data were used under license for the current study and are not publicly available. However, data are available from the authors upon reasonable request and with permission of the TidalHealth Institutional Review Board (IRB).

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